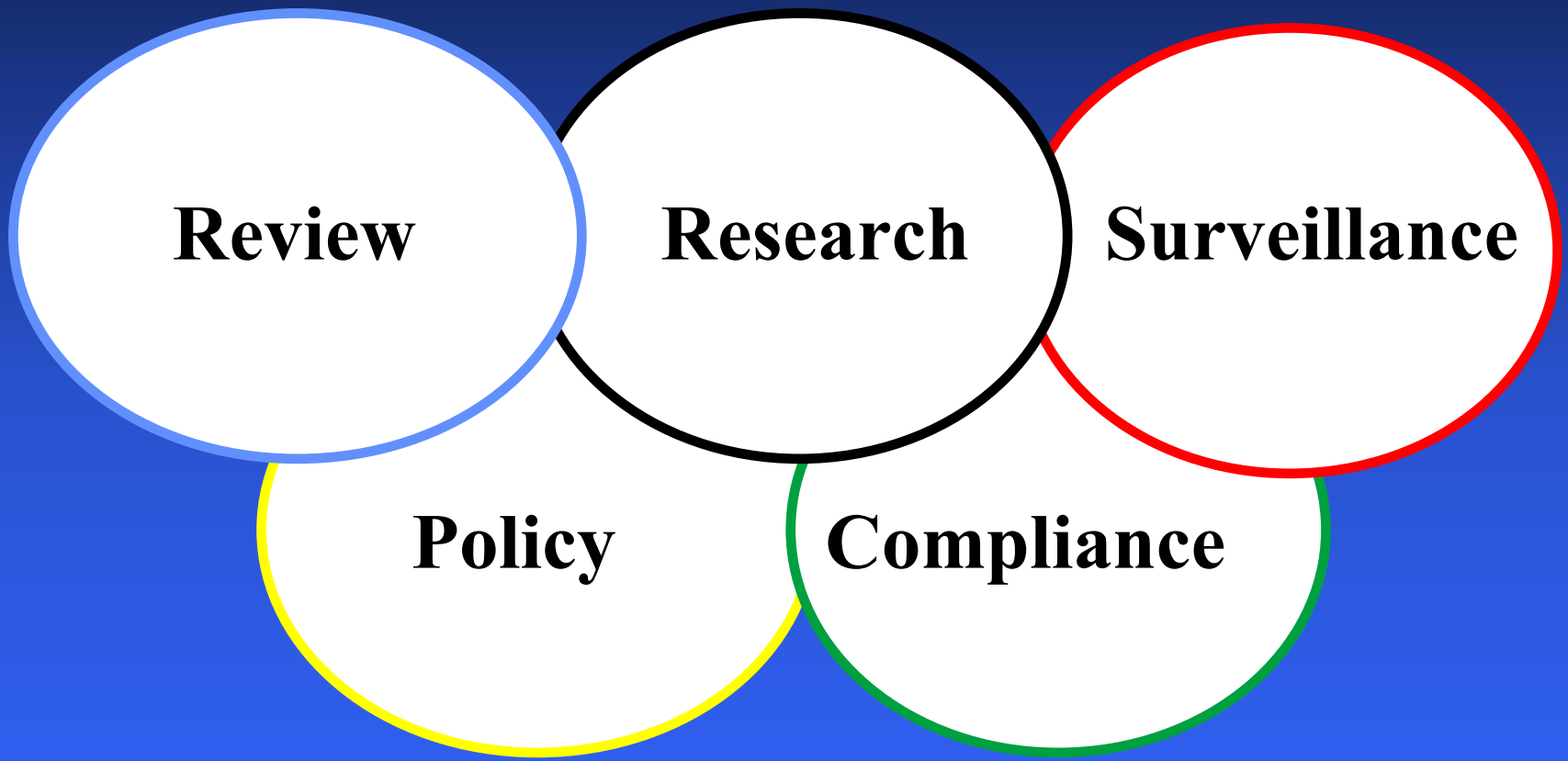
CBER Update

International Conference on Drug Development
Austin, TX
February, 2003

Mark A. Elengold
Deputy Director, Operations
Center For Biologics Evaluation and Research
Food and Drug Administration

CBER Regulation

Based on Sound Science, Law, and Public Health Impact

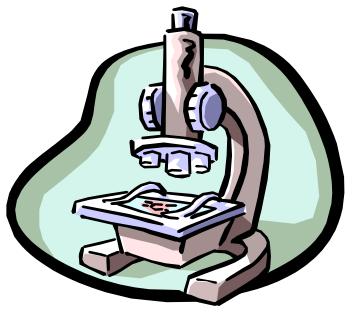


Shepherding Safe and Effective Products

Regulatory Research

FDA

Bench **Bedside** **Marketplace**



BASIC

Translational Research

NIH
Academia
Industry

APPLIED

Pharmaceutical Research

Industry

SAFETY & QUALITY

C B
E R

The Regulatory Pendulum

Centralization

Enforcement

Legal emphasis

Privatization

Process

Decentralization

Education

Science-based

Government

Content

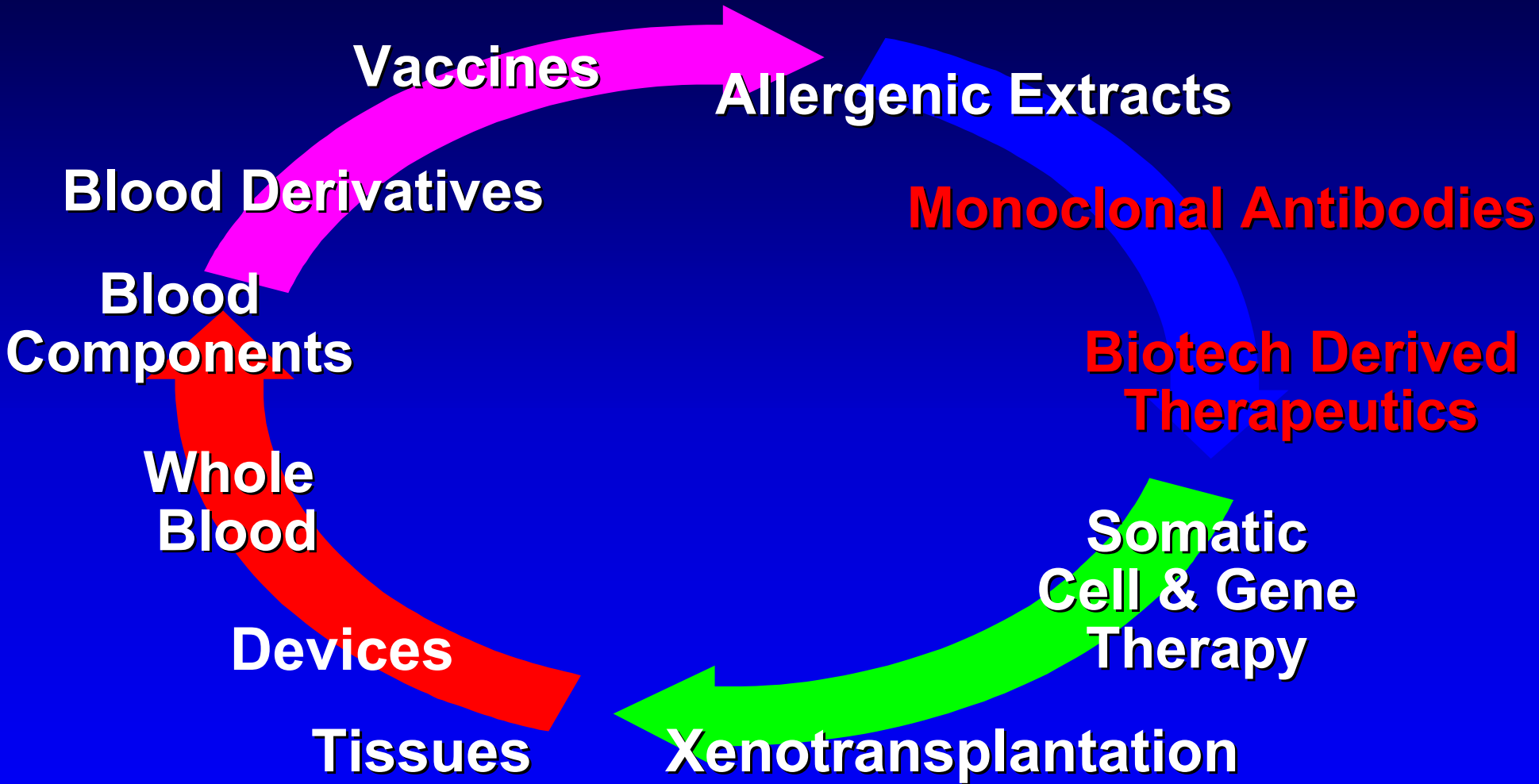
Improving Operations of Team Biologics

- Adopt internal quality management system
- Develop metrics to determine impact on industry
- Standardize training and qualifications of Core Team members
- Risk-based work planning
- Increased communications between headquarters and field

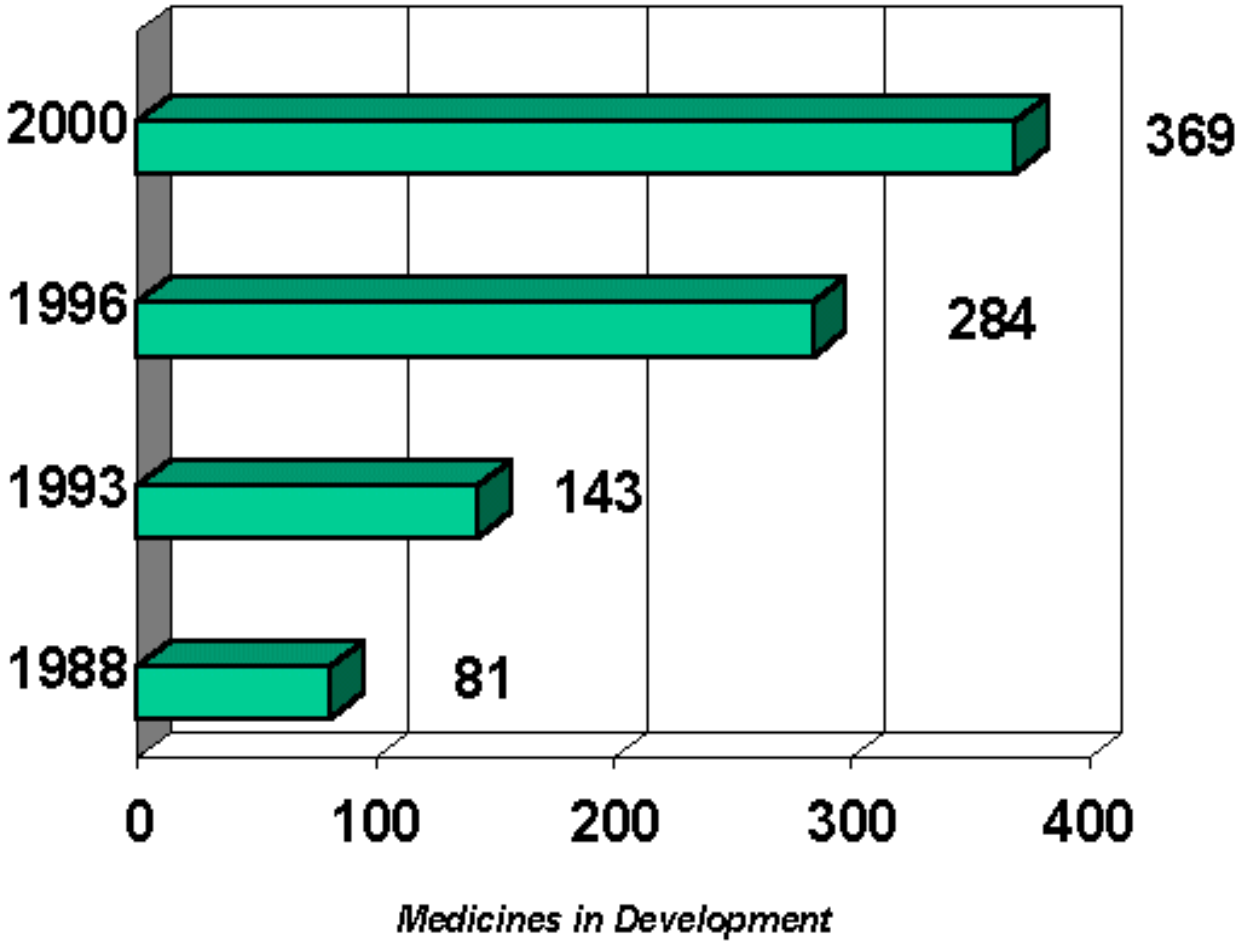
Product Specialists

- **Exploring possible approaches to include product and technical specialists on inspection teams**
  - **Product Specialists already participate on Team Biologics inspections**
- **Enhance technical quality and consistency of inspections**
- **Facilitate adoption of innovative manufacturing technologies**

BIOLOGICAL PRODUCTS REGULATED BY CBER

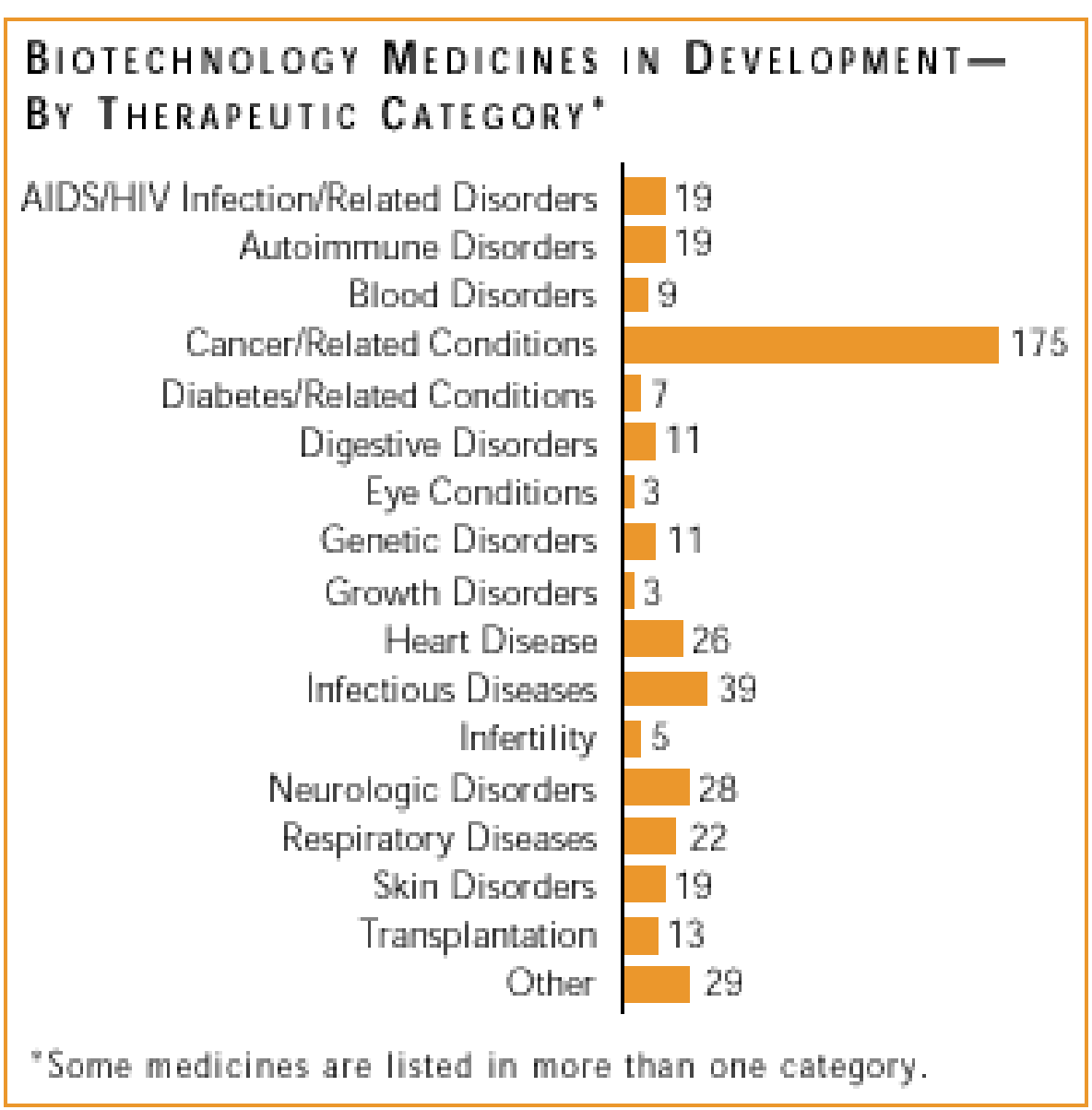


Biotechnology Medicines in Development Over the Years



The Pace of Biotechnology

A 2000 survey by PhRMA found 369 Products defined as "biotechnology medicines" in the pipeline. These use substances produced in the body to counter disease.



Commissioner's Priorities

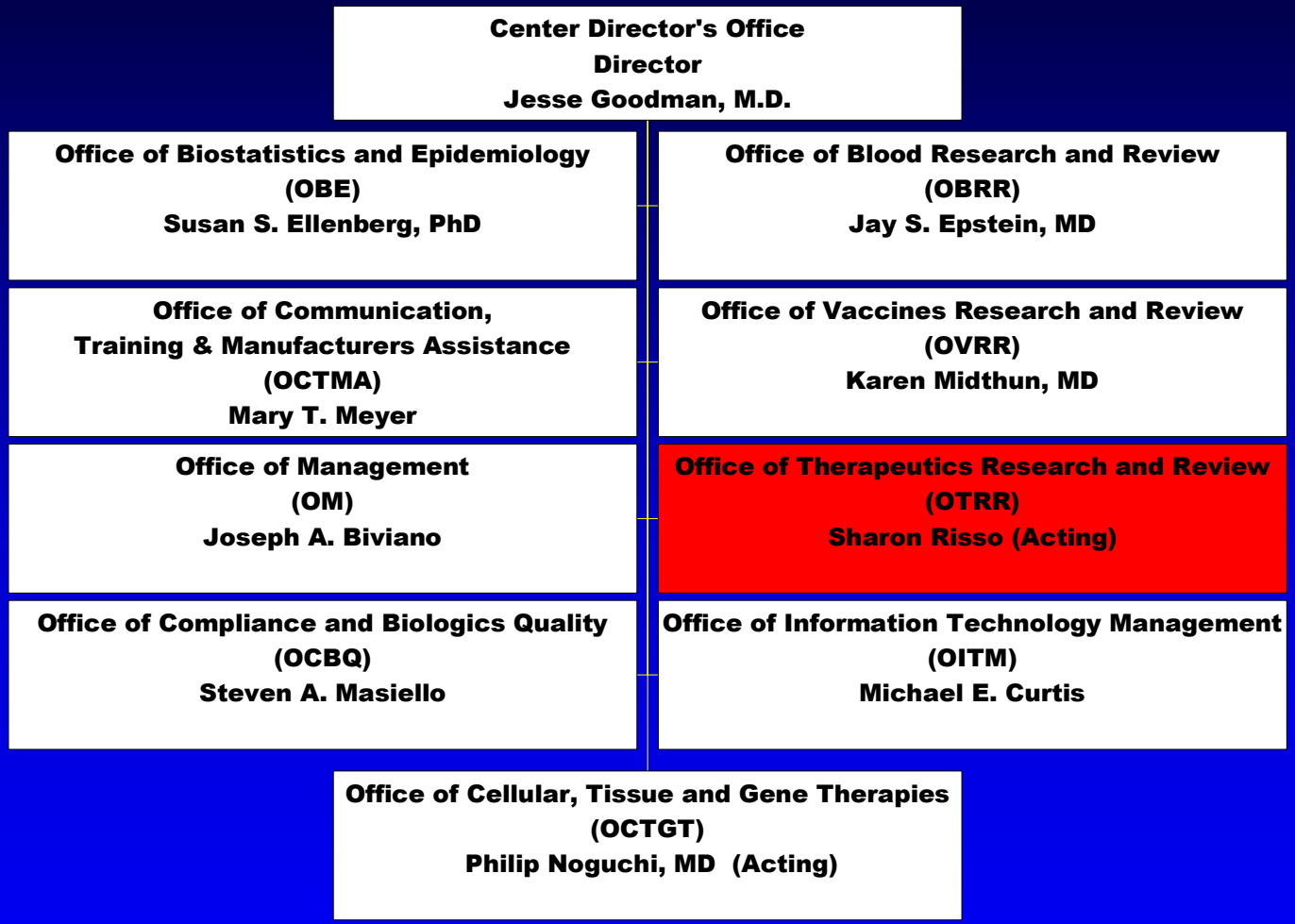
- **Strong FDA**
- **Risk Management**
- **Decrease Medical Errors and AEs**
- **Better informed constituents**
- **Counter-terrorism**

All highly pertinent to CBER missions and products, including blood

CBER CHALLENGES 2003

- **Organizational Changes**
- **New Performance Goals**
- **New Technologies**
- **International Harmonization**
- **E-business**
- **Counterterrorism**
- **Strong Regulatory Research Programs**

CBER Organization



What's Going

Monoclonal antibodies

Cytokines, growth factors, enzymes, interferons -- (including recombinant versions)

Proteins intended for therapeutic use that are extracted from animals or microorganisms (except clotting factors

Other therapeutic immunotherapies

What's Staying

- Monoclonal antibodies, cytokines, growth factors, or other proteins when used solely as an ex vivo constituent in a manufacturing process / when used solely as a reagent in the production of a product that is under the jurisdiction of CBER
- Viral-vectored gene insertions (i.e., "gene therapy")
- Products composed of human or animal cells or from physical parts of those cells

What's Staying (continued)

- Plasma expanders
- Allergen patch tests
- Allergenics
- Antitoxins, antivenins, and venoms
- In vitro diagnostics
- Vaccines
- Toxoids and toxins intended for immunization

The OTRR, CBER record

- **Science-based regulation of biologic therapeutics at OTRR has played a central role in the development and availability of safe and effective products of biotechnology that are revolutionizing medicine.**
- **OTRR scientists/physicians work independently of but closely with regulated biotechnology.**
  - **Extraordinary number of meetings**
  - **Timely, science based guidance**
- **OTRR scientists/physicians have provided international leadership in the science-based regulation of biotechnology products.**

The OTRR, CBER record (continued)

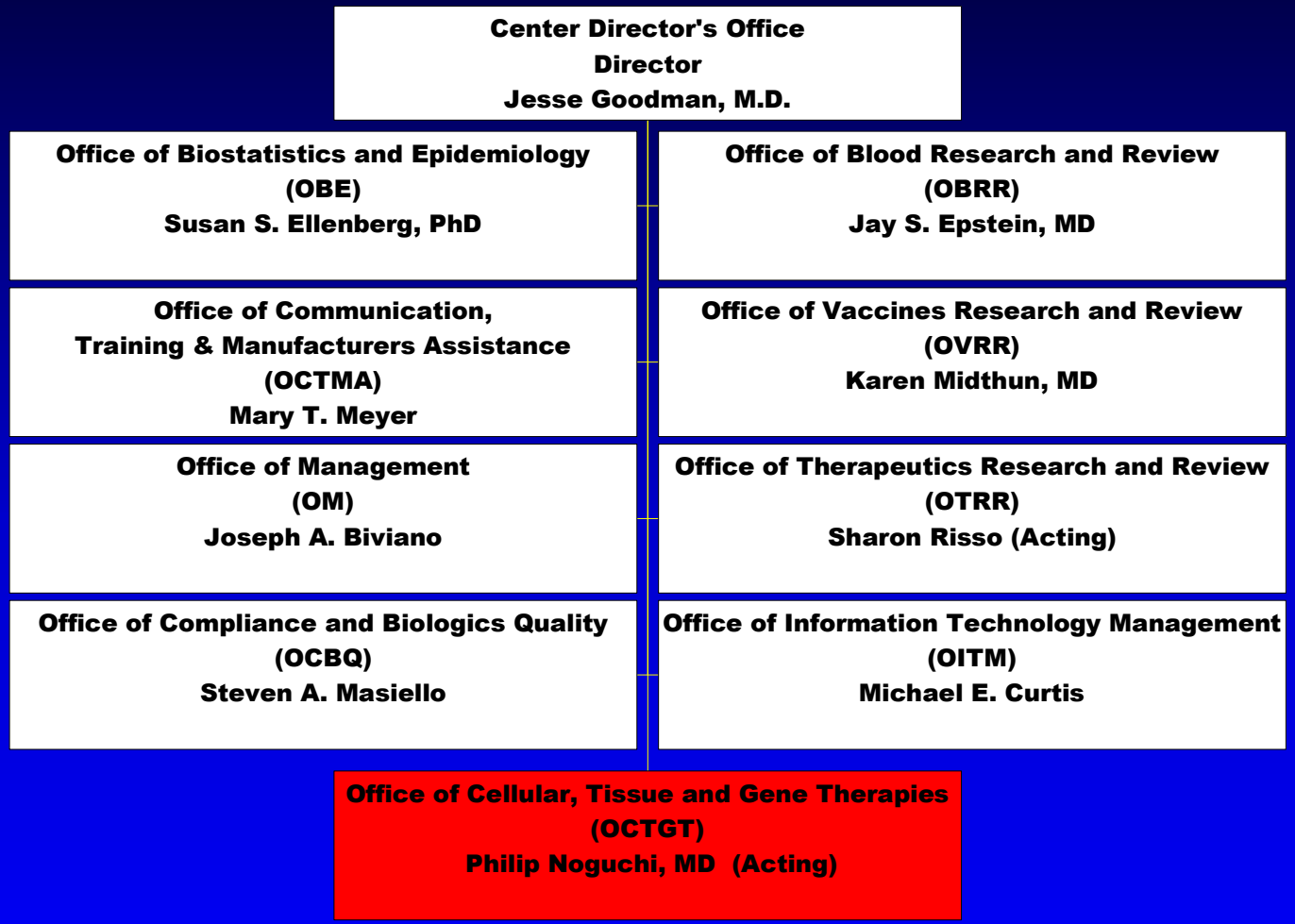
- The number of new product approvals is increasing.
- Despite the complexity and novelty of biotechnology products, review times and approval times compare favorably with those for other types of drugs.
- Biological therapeutics are often available first in the U.S.
- There has ***never*** been need to recall an OTRR-approved biotechnology drug due to safety concerns.

Number of Cycles to Approval

- From CY 1995-2001, OTRR approved 41% of the original BLAs submitted with 1 cycle
- 19% took 3 or more cycles
- Numbers are comparable to NMEs approved during this same time period

Office of Cellular, Tissue, and Gene Therapies (OCTGT)

CBER Organization



Office of Cellular, Tissue, and Gene Therapies

Dr. Philip Noguchi, (Acting) Office Director

Dr. Joyce Frey-Vasconcells,(Acting) Deputy Office Director

Regulatory Management Staff

(Acting) Chief, Ms. Andrea Wright

Division of Cellular & Gene Therapies
Dr. Raj Puri, (Acting) Director

Division of Human Tissues
Dr.Ruth Solomon, (Acting)Division Director

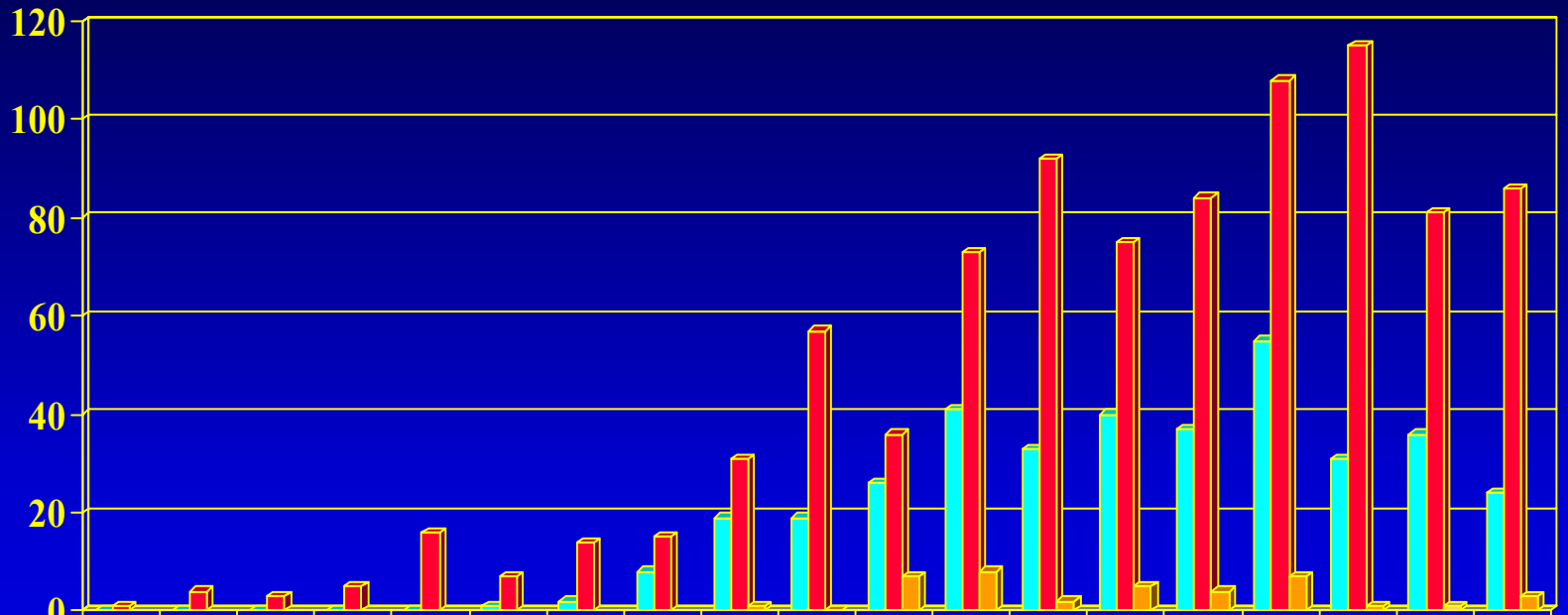
Division of Clinical Evaluation & Pharmacology/Toxicology
(Vacant)

Why?

- **Increase in regulatory activities in the areas of cellular and tissue-based products, gene therapies, and all forms of stem cell transplantation.**
- **Consolidation of products into one office**
  - **Products getting more complex**
  - **New science advances**
  - **Need for seamless and transparent coordination and communication**

Gene Therapy, Somatic Cell Therapy, Xenotransplantation INDs/IDEs

Received FY 1984 - FY 2002



	FY84	FY85	FY86	FY87	FY88	FY89	FY90	FY91	FY92	FY93	FY94	FY95	FY96	FY97	FY98	FY99	FY00	FY01	FY02
GT INDs	0	0	0	0	0	1	2	8	19	19	26	41	33	40	37	55	31	36	24
SCT INDs/IDEs	1	4	3	5	16	7	14	15	31	57	36	73	92	75	84	108	115	81	86
Xeno INDs									1	0	7	8	2	5	4	7	1	1	3

Note: A total of 7 INDs were for Xeno and GT, and are included in the counts for both.

(148ir)RIMS:10/03/02

CBER

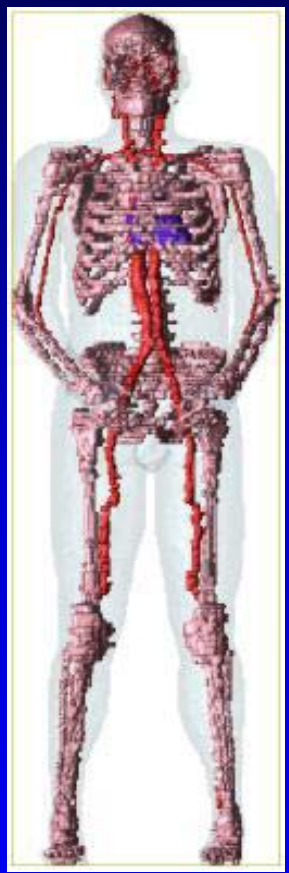
Mission

- **Regulatory and review responsibilities:**
  - **Tissues**
  - **Cellular and Tissue-based products**
  - **Gene Therapies**
  - **Xenotransplantation**
  - **Unique assisted reproduction (ooplasm transfer)**
  - **Combination Products containing living cells/tissues**
- **Assure safety, identity, purity and potency of novel products**

FDA/CBER and Tissues

Proposed Approach to Tissues

- **Comprehensive Wide spectrum of products**
- **Protect public health**
- **Permit innovations without unnecessary burden**
- **TIERED; RISK-BASED**



Public Health and Regulatory Concerns

- Transmission of communicable disease
- Processing controls to prevent contamination
- Clinical safety and efficacy
- Promotional claims/labeling
- Monitoring and information sharing, quality improvement with industry

Implementation

Three rules:

- **One Finalized**
  - **Establishment Registration and Listing**
    - 63 FR 26744, effective 4/4/01(for currently regulated tissues)
    - Effective date for remaining products to coincide with effective dates for other two rules
- **Two Proposed**
  - **Suitability Determination for Donors**
    - 64 FR 52696 Sept. 30, 1999
  - **Current Good Tissue Practice (cGTP)**
    - 66 FR 1508 Jan. 8, 2001

CBER

Performance-Based Organization

- Prescription Drug User Fee Program
- Medical Device User Fee Modernization Act
- Blood and Tissue Safety

CBER Biologics License Application Approvals for Biotechnology Products 1981-2002

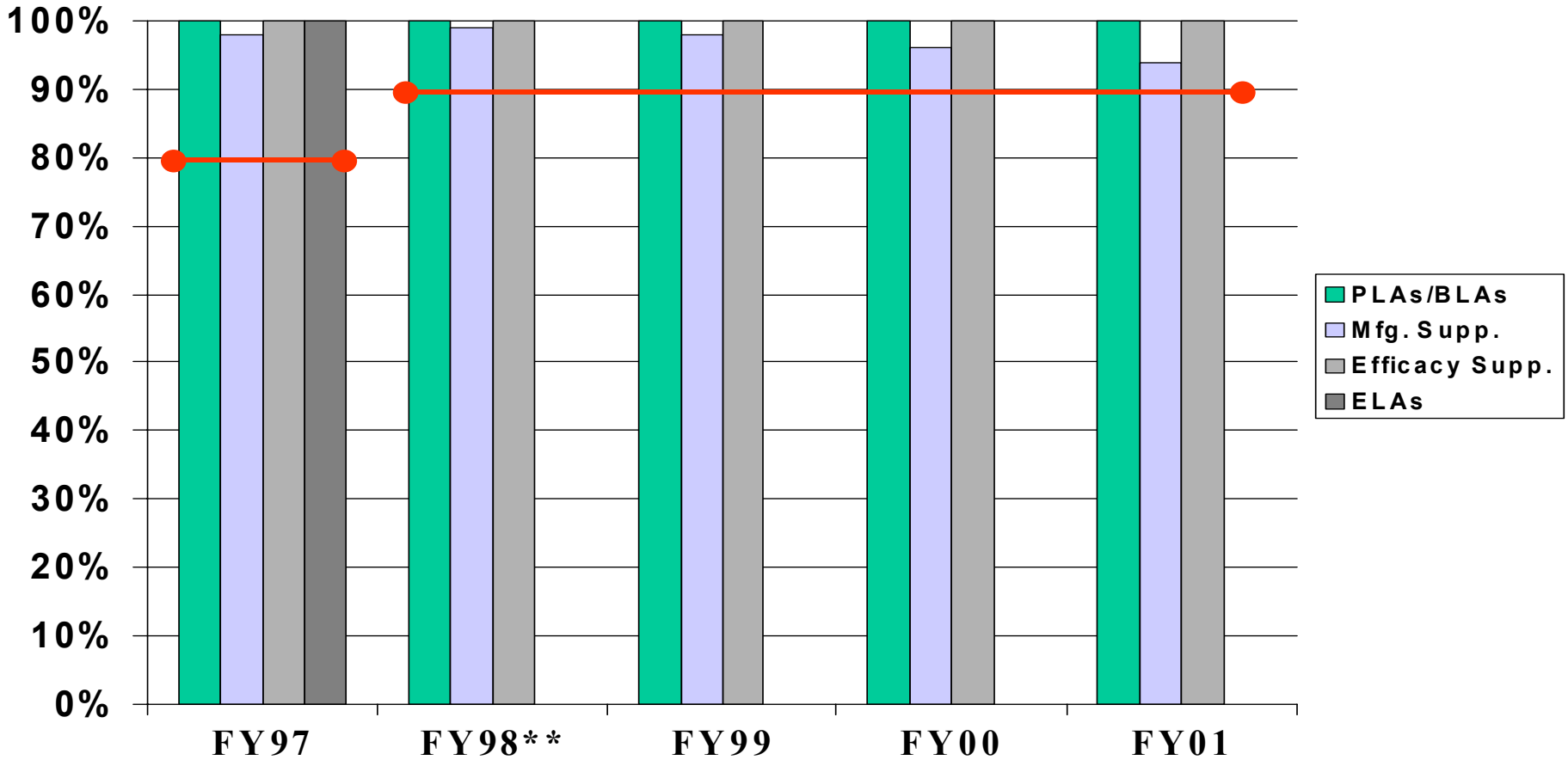
Years	Therapeutics*	Vaccines	IVD	Total
1981-85	0	0	23	23
1986-90	6	2	35	43
1991-95	13	0	59	72
1996-00	26	2	26	54
2000-02	11	2	5	18
Total	56	6	148	210

CBER User Fee Review Performance

License Applications and Supplements

% of First Actions Within Goal*

By Cohort Fiscal Years 1997-2001



* PDUFA Performance Goals: FY97 - FY01=90% (Indicated by Red Lines)
** Beginning in FY98 ELAs were no longer included in PDUFA goals

(253bp)RIMS 12/26/02

CBER PDUFA II Procedural and Processing Goals Performance (as of December 31, 2002)

Regulatory Meetings Management										
			Actions Within Goal			Actions Overdue				
Fiscal Year	Goal	Meeting Requests Received	Completed	Pending	Total	Completed	Pending	Total	% Completed Within Goal[1]	*PDUFA Goal*
FY 1999	Response	387	283	0	283	104	0	104	73%	*70%*
	Held	364	321	0	321	43	0	43	88%	
	Minutes	328	282	0	282	46	0	46	86%	
FY 2000	Response	312	302	0	302	10	0	10	97%	*80%*
	Held	294	277	0	277	14	3	17	94%	
	Minutes	251	229	0	229	19	3	22	91%	
FY 2001	Response	388	379	0	379	9	0	9	98%	*90%*
	Held	341	330	0	330	10	1	11	97%	
	Minutes	293	286	0	286	7	0	7	98%	
FY 2002	Response	415	401	0	401	12	2	14	97%	*90%*
	Held	374	360	0	360	9	5	14	96%	
	Minutes	335	317	2	319	6	10	16	95%	

[1] - of those that have reached the goal date

CBER

CBER PDUFA II Procedural and Processing Goals Performance – *cont.*
(as of December 31, 2002)

Special Protocol Assessment

Fiscal Year	Protocol Review Requests Received	Actions Within Goal			Actions Overdue			% Completed Within Goal[1]	*PDUFA Goal*
		Completed	Pending	Total	Completed	Pending	Total		
FY 1999	0								*60%*
FY 2000	0								*70%*
FY 2001	1	1	0	1	0	0	0	100%	*80%*
FY 2002	4	4	0	4	0	0	0	100%	*90%*

Major Dispute Resolution

Fiscal Year	Dispute Resolution Requests Received	Actions Within Goal			Actions Overdue			% Completed Within Goal[1]	*PDUFA Goal*
		Completed	Pending	Total	Completed	Pending	Total		
FY 1999	1	1	0	1	0	0	0	100%	*70%*
FY 2000	0								*80%*
FY 2001	2	2	0	2	0	0	0	100%	*90%*
FY 2002	4	4	0	4	0	0	0	100%	*90%*

Responses to Clinical Holds

Fiscal Year	Responses to Clinical Holds Received	Actions Within Goal			Actions Overdue			% Completed Within Goal[1]	*PDUFA Goal*
		Completed	Pending	Total	Completed	Pending	Total		
FY 1998	22	18	0	18	4	0	4	82%	*75%*
FY 1999	77	73	0	73	4	0	4	95%	*90%*
FY 2000	89	87	0	87	2	0	2	98%	*90%*
FY 2001	125	115	0	115	10	0	10	92%	*90%*
FY 2002	121	118	0	119	3	0	3	98%	*90%*

[1] - of those that have reached the goal date

CBER Review Performance
FY 2002 Cohort of User Fee Applications

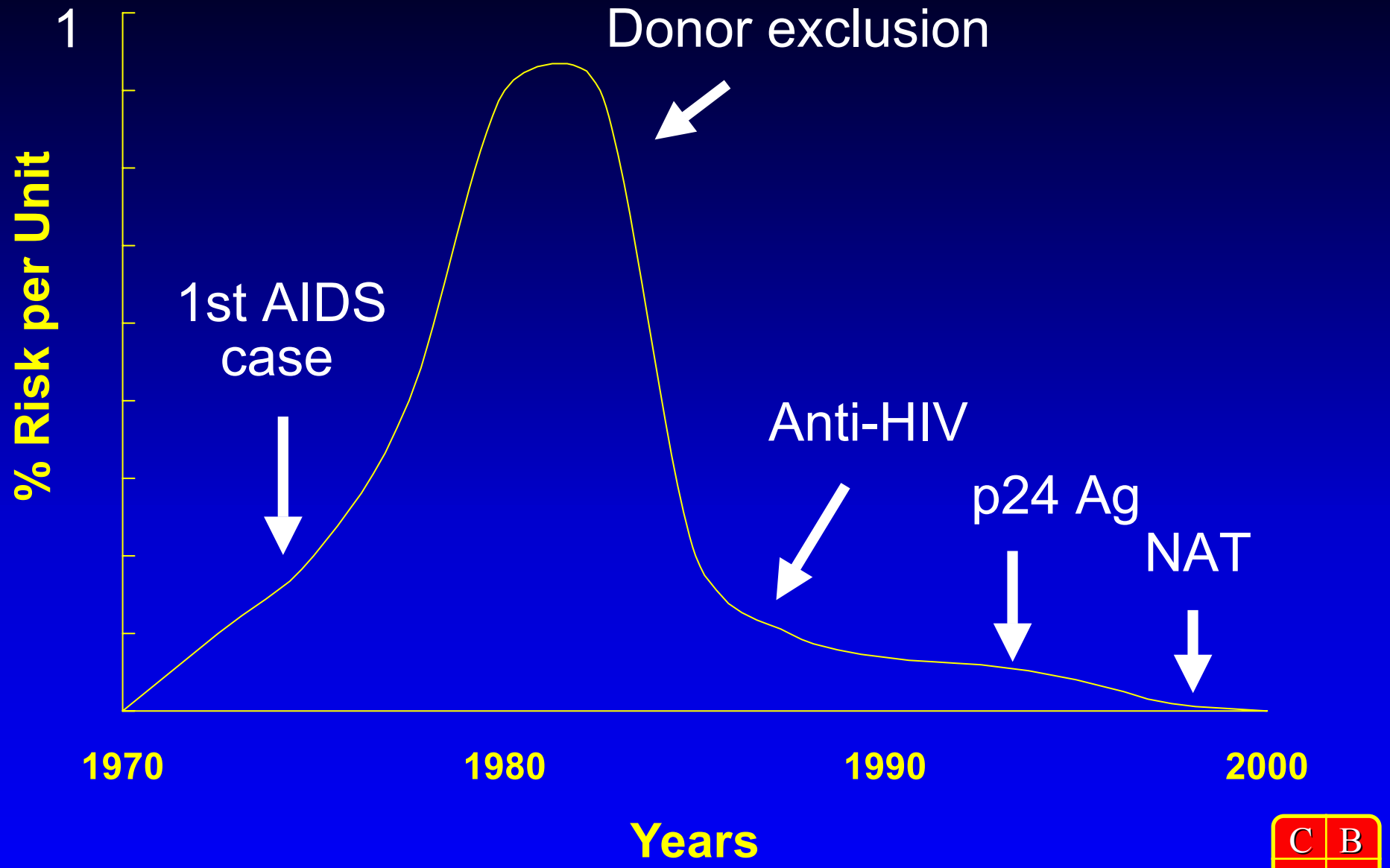
Application Types	Numbers				Percent of Actions	
	Submitted	Filed	AP	RTF, UN, or WF	Within Goal	Overdue
New Products	10	9	0	1	22%	0%
Effectiveness Supplements	11	11	2	0	45%	0%
Manufacturing Supplements	748	748	378	0	74%	1%

AP=Approved, RTF=Refuse To file, UN=Unacceptable For Filing, WF=Withdrawn Before Filing

Emerging Infectious Diseases and Blood *and Tissues*: The Challenge Continues

Blood Safety in the 21st Century

- New Blood Screening Tests, e.g. West Nile Virus
- Pathogen Inactivation
- Oxygen Carriers/Blood Substitutes



Data provided by Michael Busch, Blood Centers of the Pacific

C B
E R

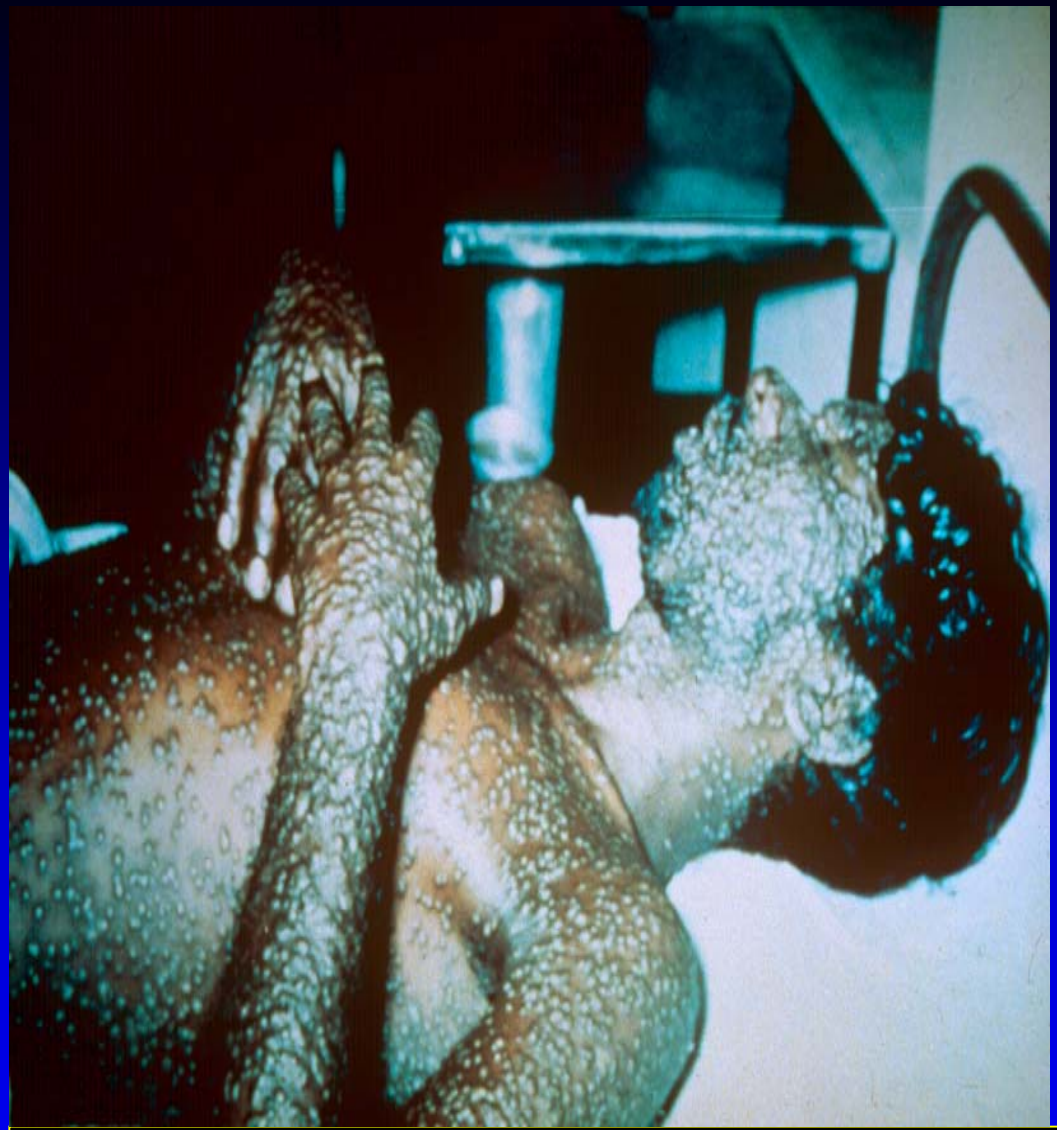
Medical Device User Fees

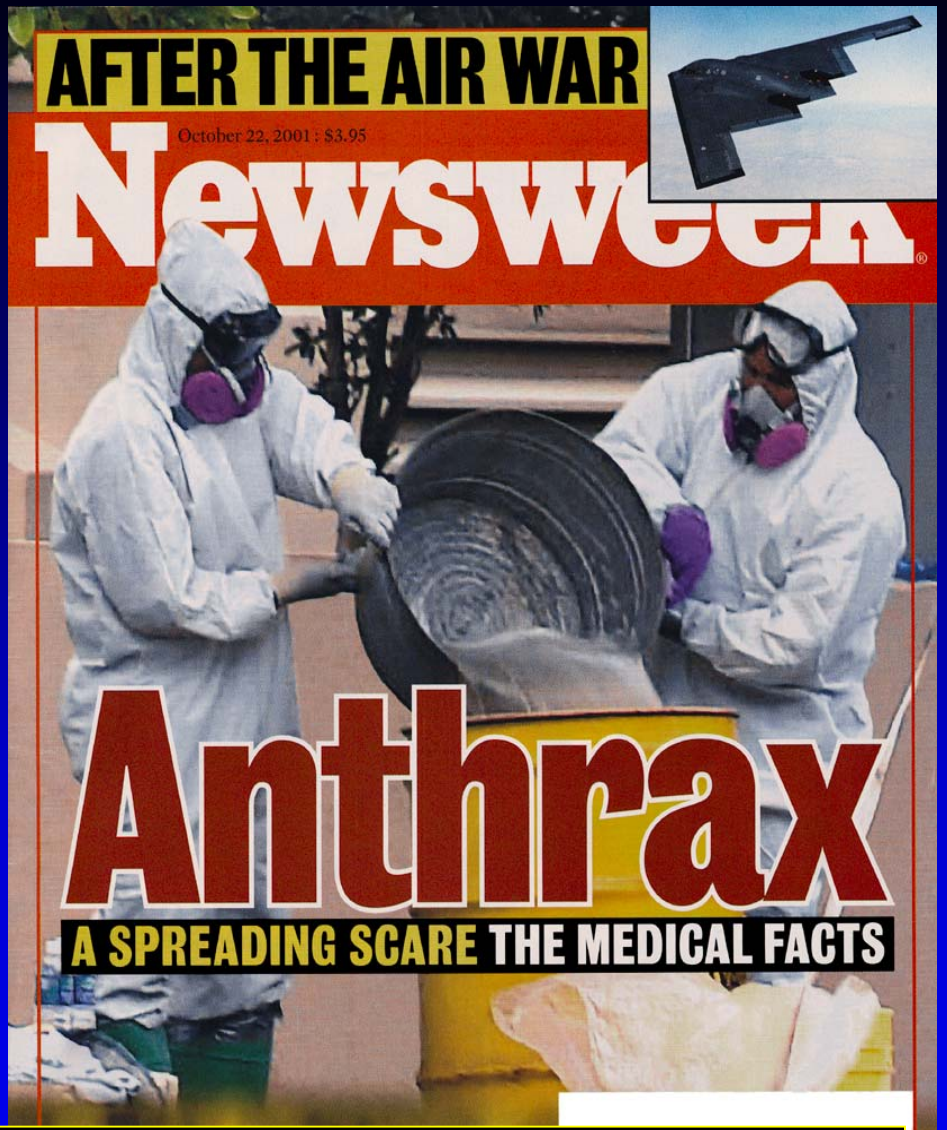
- Fees for original applications and some supplements
- $25.1 million in fee revenues during FY 2003 plus $15 million additional appropriations
- First year fees $154,000 for a premarket applications to $2,187 for a 510(k)
- Reduced fees to protect small businesses

Performance Goals

- **Overall, aim to improve performance 25%**
- **Goals defined in letter from Secretary Thompson to Congress**
- **Combination of cycle goals and decision goals (PMAs, 510(k)s)**
- **Measured in FDA days**

C B
E R





COUNTER- BIOTERRORISM

Approaches to Speed Product Availability or Licensure

- Early and frequent consultation between sponsor, end user (if different) and FDA
- Availability for emergency use under IND
- Fast track and accelerated approval processes
- Priority review
- Approval under "Animal Rule"
- Careful attention to risk:benefit and risk management issues
- Incentives (existing: orphan, new: push or pull)

Regulation and BT Products: What is the value added?

- **As for other medical products (but perhaps even more important): need for consistent and objective protection of the public's safety** *and need for trust*
  - **Heat of the moment(s): sense of emergency and national crisis; dangers of decisions made in panic mode**
  - **Almost all parties (even sister agencies, academia) can become invested in product development and availability, financially and/or emotionally**
  - **Need to identify where speed and innovation do not compromise safety or effectiveness**
  - **When things go "wrong" (or even if someone just thinks they did), few will remember the crisis**

Key Progress in Information Management Initiatives

- Paperless BLAs and NDAs since 6/00
- EDR in place and being upgraded
- Infrastructure: Standard Platform in place with upgraded network
- Pilot Project: Secure e-Mail
- RMS-BLA implemented/being upgraded
- Working with CDER on ICH e-CTD
- Electronic Submission Guidance

Electronic Submissions Guidance

- Guidance for Industry: Providing Regulatory Submissions in Electronic Format-General Considerations
- Revised Guidance for Industry: Providing Regulatory Submissions to CBER in Electronic Format - BLA, PLA, ELA, NDA
- Draft Guidance for Industry: Electronic Records; Electronic Signatures; Validation; Glossary of Terms
- Draft Guidance for Industry: Prescription Drug Advertising and Promotional Labeling
- Draft Guidance for Industry: Pilot Program for Electronic Investigational New Drug (eIND) Applications for Biological Products

CBER e-Business

- CBER is the first Center to accept fully electronic regulatory documents with digital signatures and automated submission and processing via ESM
- The EDR, ESM, and e-Routing are a complete, robust set of review tools to meet reviewer needs, developed in conjunction with the reviewer community
- CBER's electronic submission infrastructure and applications may form the core of an overall FDA electronic submission toolset
- The CBER Electronic Submissions program is robust and has made great strides since its inception in 1996

New Technologies

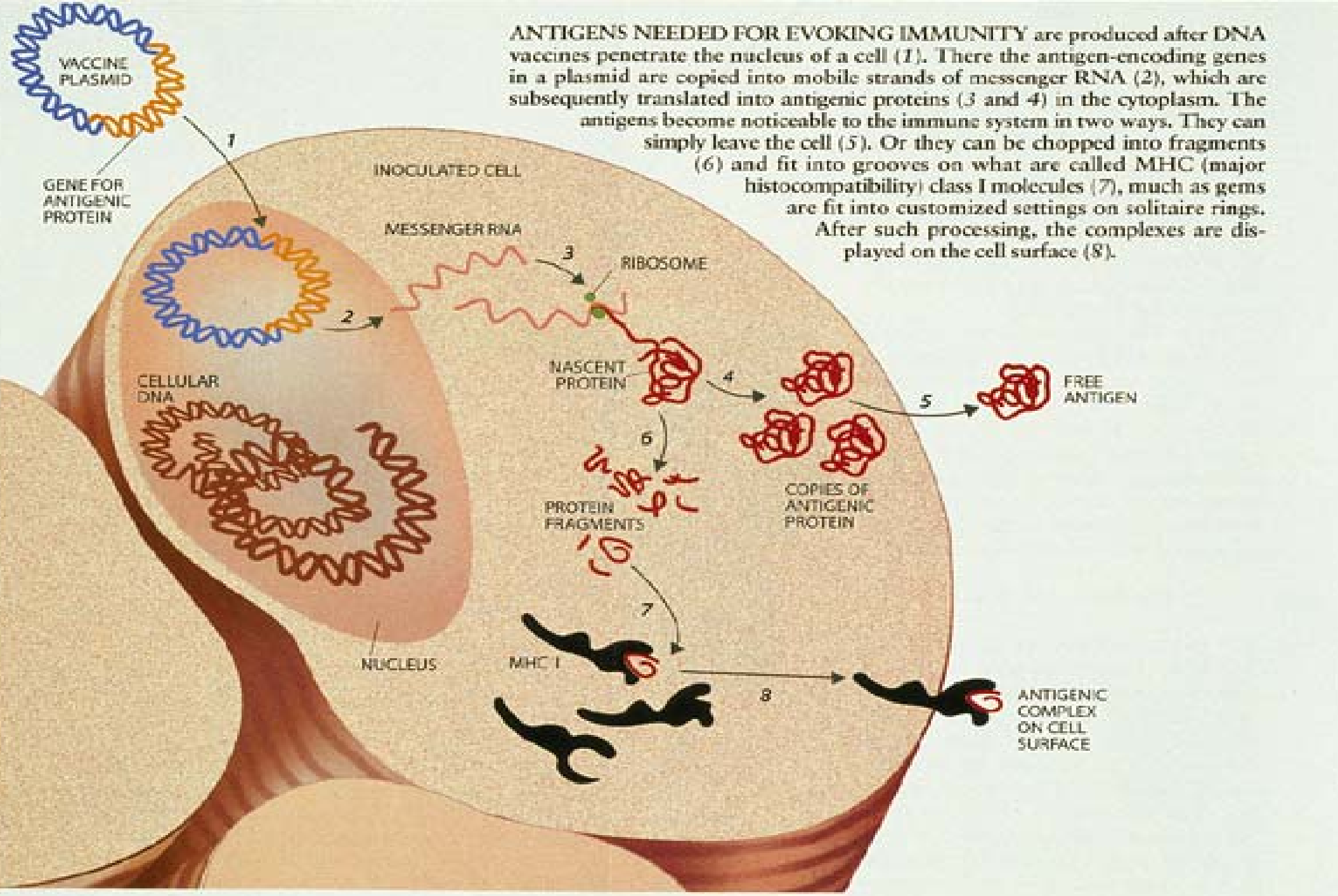
- New Vaccines
- Cellular and Gene Therapies
- Proteomics and Genomics
- Transgenics: Plants and Animals
- New Diagnostics for Blood and Tissue Safety

C B
E R

Vaccines of the 21st Century

New Vaccines

- Nucleic Vaccines
- Live Attenuated Vaccines
- Combination Vaccines
- Therapeutic Vaccines



ANTIGENS NEEDED FOR EVOKING IMMUNITY are produced after DNA vaccines penetrate the nucleus of a cell (*1*). There the antigen-encoding genes in a plasmid are copied into mobile strands of messenger RNA (*2*), which are subsequently translated into antigenic proteins (*3* and *4*) in the cytoplasm. The antigens become noticeable to the immune system in two ways. They can simply leave the cell (*5*). Or they can be chopped into fragments (*6*) and fit into grooves on what are called MHC (major histocompatibility) class I molecules (*7*), much as gems are fit into customized settings on solitaire rings. After such processing, the complexes are displayed on the cell surface (*8*).

Tissues, Cells and Related Products

- Conventional Banked Tissues for Transplantation
- Gene Therapy
- Reproductive Cells
- Human Reproductive and Therapeutic Cloning
- Somatic Cell Therapies, e.g. Stem cells
- Xenotransplantation (separate Action Plan)

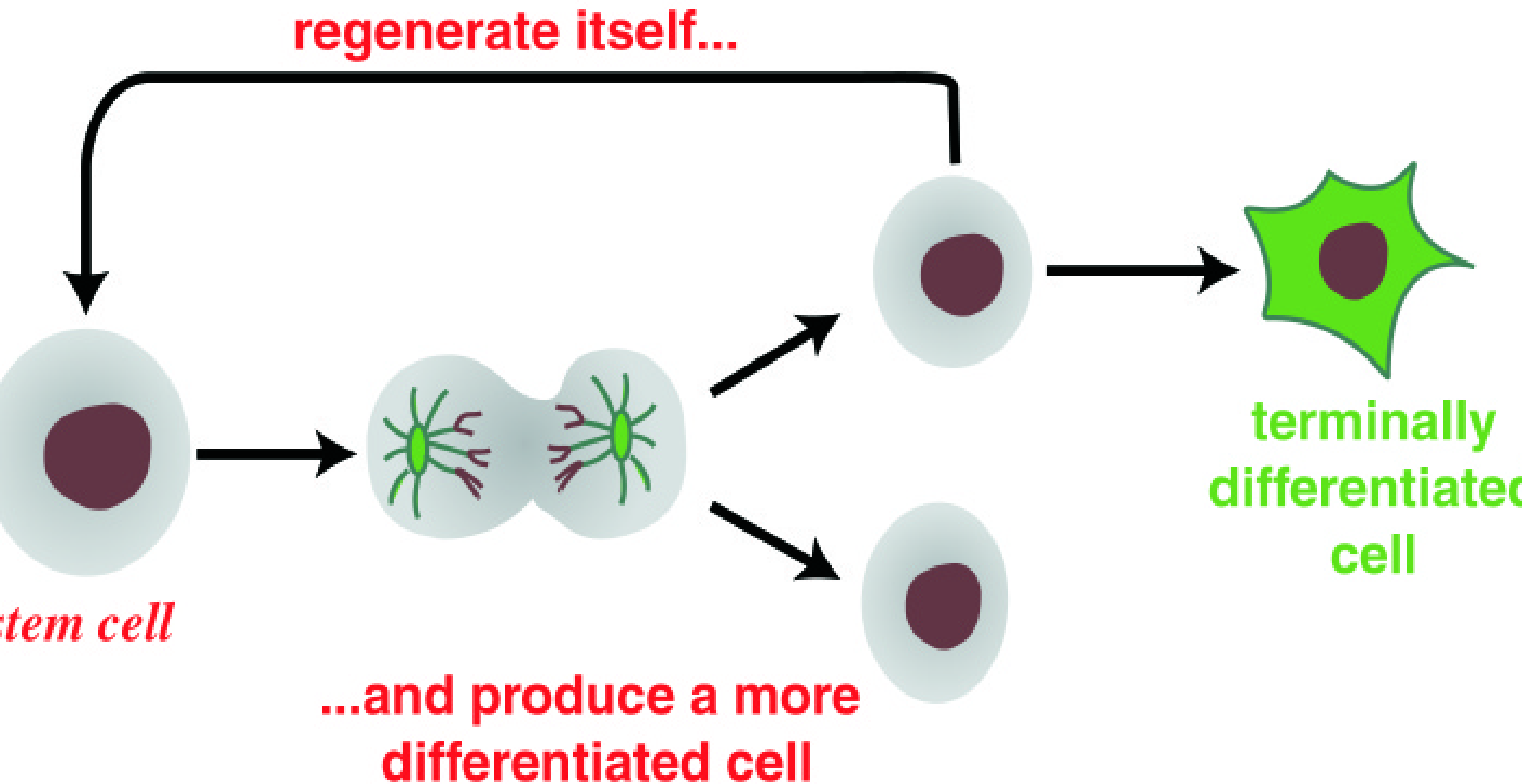
Novel Cell Products

Regenerative Medical Products

- Stem cells e.g. embryonic, mesenchymal
- Tissue Engineering

C B
E R

A ***stem cell*** is one that can

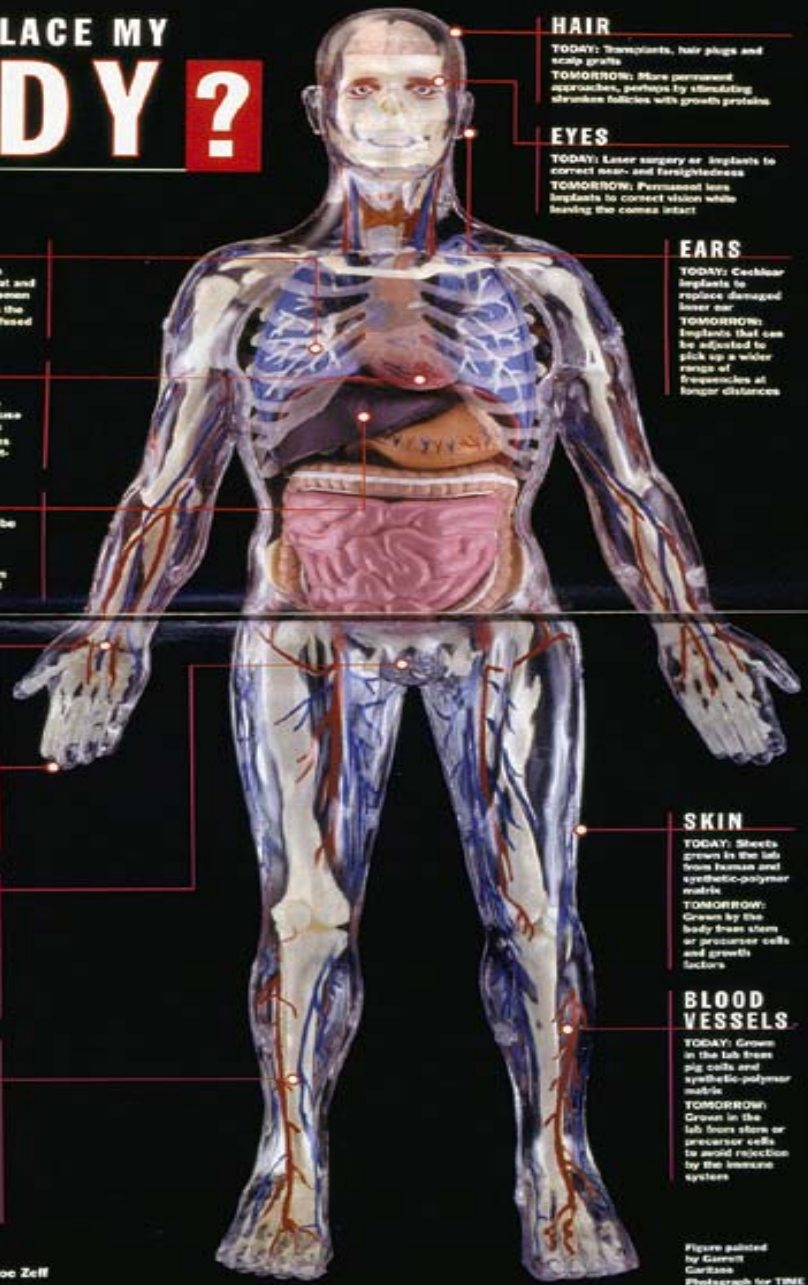


Cell and Tissue Therapies, e.g.

- Hematopoietic stem cells
- Embryonic stem cells
- Expanded lymphocytes
- Assisted reproductive technologies
- Tissue engineering
- Pancreatic islet cells
- Hepatocytes
- Cartilage
- Xenotransplantation

visions 21 health & environment

CAN I REPLACE MY BODY?



HAIR

TODAY: Transplants, hair plugs and scalp grafts

TOMORROW: More permanent approaches, perhaps by stimulating shrunken follicles with growth proteins

EYES

TODAY: Laser surgery or implants to correct near- and farsightedness

TOMORROW: Permanent lens implants to correct vision while leaving the cornea intact

BREAST

TODAY: Breasts are reconstructed with saline sacs or with living tissue, using fat and muscle from the back, buttocks or abdomen

TOMORROW: Breasts may be grown in the lab from a patient's own fat cells and infused back through keyhole slits in the chest

HEART

TODAY: Bypasses, angioplasty and transplants to keep blood flowing to the heart muscle. Doctors are beginning to use gene therapy to grow new blood vessels

TOMORROW: Growing functional patches of heart muscle or coaxing existing heart-muscle cells to repair themselves

ORGANS

TODAY: Small slivers of liver tissue can be grown in the lab from one of the many types of liver cells, but they are not yet ready for transplant

TOMORROW: Heart, liver, kidneys grown from stem cells in vitro and transplanted into the body

NERVES

TODAY: Grown in the lab from pig cells and synthetic-polymer matrix

TOMORROW: Regenerated from stem or precursor cells in the body

LIMBS

TODAY: Prosthetics wired to peripheral nervous system

TOMORROW: Prosthetics wired directly to motor portions of the brain to improve control and simulate the sensations of touch, pain, etc.

PENIS

TODAY: Penile implants and medication to maintain erection. Surgery to reattach a severed penis; skin grafts to recover urinary, but not sexual, function if penis is not recovered

TOMORROW: Genetically engineered tissue grown in the lab and attached for final growth to form fully functional penis

BONE AND CARTILAGE

TODAY: Injection of bone growth factors into jaw and other fracture areas. Researchers can also grow cartilage in the lab in thin sheets, but it's too weak to be functional in the body

TOMORROW: Coaxing the body to grow bone and cartilage on biodegradable scaffolds infused with a mix of stem cells and growth factors

EARS

TODAY: Cochlear implants to replace damaged inner ear

TOMORROW: Implants that can be adjusted to pick up a wider range of frequencies at longer distances

SKIN

TODAY: Sheets grown in the lab from human and synthetic-polymer matrix

TOMORROW: Grown by the body from stem or precursor cells and growth factors

BLOOD VESSELS

TODAY: Grown in the lab from pig cells and synthetic-polymer matrix

TOMORROW: Grown in the lab from stem or precursor cells to avoid rejection by the immune system

By Alice Park; TIME Graphic by Joe Zeff

Figure painted by Garrett Gerlach. Photograph for TIME by Ted Thai

Xenotransplantation Initiatives

- Xenotransplantation Action Plan (XAP)
- Secretary's Advisory Committee on Xeno (SACX)
- Xeno Sub-Committee of the Biological Response Modifiers Advisory Committee (BRMAC)
- National Xenotransplantation Registry and Database

Transgenics

- **Transgenic Plant and Animal Products**
  - **Vaccines**
  - **Monoclonal Antibodies**
  - **Therapeutic Proteins**

Biosource researchers used tobacco plants as an alternative mechanism for antibody production. The researchers removed malignant B cells from laboratory mice and then isolated the gene for a small piece of the surface markers that are specific to these cells. They inserted this gene into tobacco mosaic virus and then infected tobacco plants.

CBER views on Genomics and Proteomics:

- Critical component of safe and effective drug development
- Basis for new drug discovery, biomarkers and surrogate endpoints for toxicity and efficacy monitoring
- Means to detect and assess chemical and biological terrorist agents

Regulatory Impact

- Vaccine assessment/potency
- Surrogate endpoints- efficacy/toxicity
- Quality control/quality assurance for product production
- New Bioassays
- Biomarkers for early detection
- Toxicity detection and prediction

Regulatory Impact (cont.)

- Discovery of new therapeutics targets
- Risk of disease recurrence
- Patient-tailored therapy. Prospective selection
- New paradigm in disease classification/characterization
- Proteomic-based epidemiology

NCI-CBER/FDA Tissue Proteomics Initiative

DISCOVERY

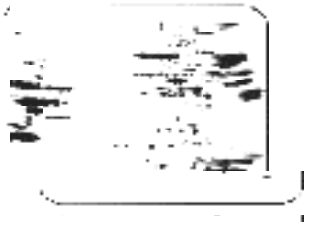
IDENTIFICATION

VALIDATION

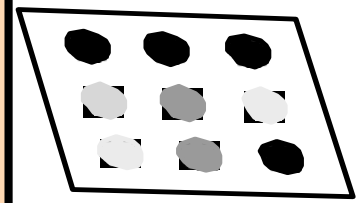
TISSUE

BODYFLUIDS

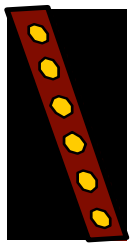
2-D GELS



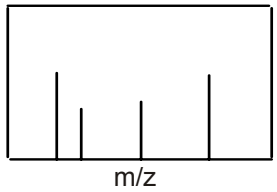
PROTEIN ARRAYS



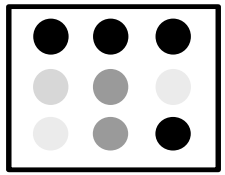
SELDI-TOF



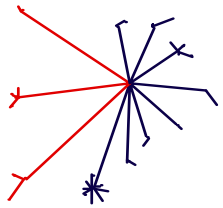
Mass Spectroscopy



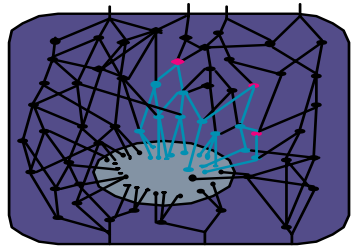
Lysate Arrays



HEURISTIC PATTERN ANALYSIS



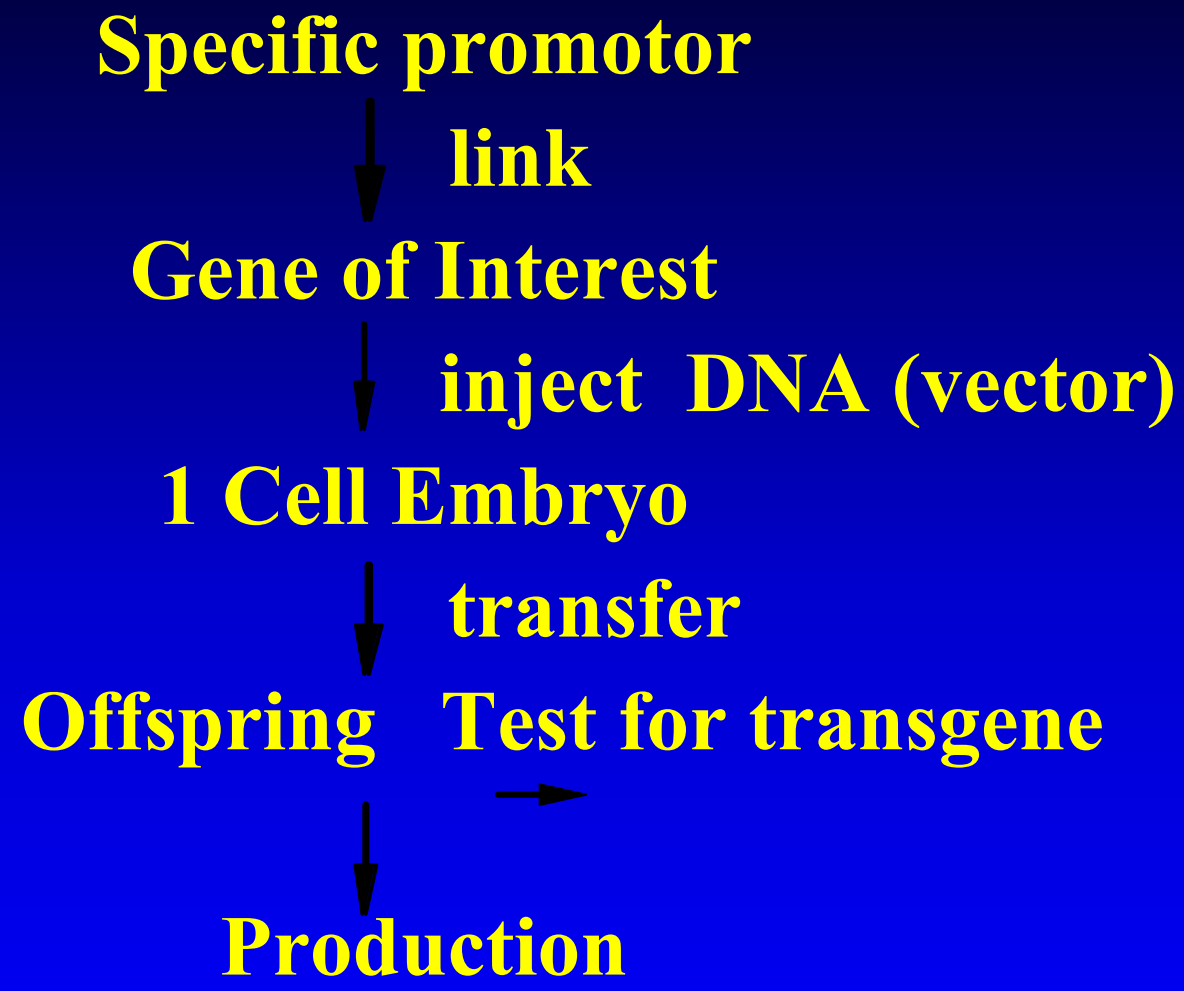
PROTEIN CIRCUIT BUILDING



Diagnostics

Targeted Therapeutics

Transgenic Animal Biological Product



FDA Regulatory Authority Over Human Cloning

International Harmonization

- International Conference on Harmonisation: Q, S, E and M topics
- World Health Organizations
- US FDA and EU bilateral
- National Institute for Biological Standards and Controls (NIBSC), United Kingdom
- Interactions with Individual Countries, e.g. Mexico, Canada, Switzerland

We're Here to Help You!

WWW.FDA.GOV/CBER

- **Email CBER:**
  - **Manufacturers: matt@cber.fda.gov**
  - **Consumers, health care professionals: octma@cber.fda.gov**
- **Phone:**
  - **800-835-4709**
  - **301-827-1800**